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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/415,795	10/08/1999	PENGBO ZHOU	HMV-043.01	5319

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EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT PAPER NUMBER

1652

DATE MAILED: 03/27/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/415,795

Applicant(s)

ZHOU ET AL.

Examiner

Elizabeth Slobodyansky

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 04 January 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4, 6--35 is/are pending in the application.
- 4a) Of the above claim(s) 12,13 and 16-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4,6-11,14,15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 17.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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### **DETAILED ACTION**

The amendment filed January 4, 2002 amending the specification to insert reference to the provisional application and sequence identifiers, canceling claim 5 and amending claims 1, 6 and 11 has been entered.

Claims 1-4 and 6-35 are pending. Claims 12, 13 and 16-35 are withdrawn. Claims 1-4, 6-11, 14 and 15 are under consideration.

Rejections and/or objections not reiterated from previous Office action are hereby withdrawn.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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Claims 1-4, 6-11, 14 and 15 are drawn to a method for targeting degradation of a polypeptide using a hybrid of a ubiquitin protein ligase polypeptide and a target polypeptide interaction domain *in vivo*.

The rejection has been explained in the Office action mailed August 6, 2001.

In sum, the hybrid protein suitable for use in a claimed method is described by broad function. The description of identifying structural and/or physicochemical characteristics related to the function is lacking and is unpredictable based on the state of the art.

Claims 1-11, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of use of Cdc4 and  $\beta$ TrCP hybrids for degradation of polypeptides in yeast and human cells, respectively, does not reasonably provide enablement for a method of use of any hybrid based on any component of ubiquitin ligase, including components of SCF other than Cdc4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection has been explained in the Office action mailed August 6, 2001.

In sum, the specification enables for a method of use of Cdc4 and  $\beta$ TrCP hybrids for degradation of polypeptides in yeast and human cells, respectively. It is not enabled

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for a method of use of any hybrid protein based on any component of any ubiquitin ligase, including components of SCF other than Cdc4.

### ***Response to Arguments***

Applicant's arguments filed January 4, 2002 have been fully considered but they are not persuasive.

It appears that Applicants argue the enablement while traversing the written description rejection. They argue that "the specification teaches that a key element to achieving success in recruiting the target polypeptide to a ubiquitin ligase is the creation of a fusion protein, an elemental aspect of genetic engineering which is well-known and, indeed, routine in the art (page 14, 3rd paragraph). This is not persuasive because the production of a fusion protein is indeed enabled by and is routine in the art. However, the description of the entire genus of said fusion protein that can be used in a claimed method is limited to Cdc4/ $\beta$ TrCP based hybrids in a host cell naturally containing other components of a ubiquitin ligase complex.

The genus of fusion proteins that comprise these hybrid molecules is a large variable genus encompassing many structurally and functionally unrelated proteins. The specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being a hybrid polypeptide

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comprising any ubiquitin ligase and any target protein interaction domain and fails to provide any structure: function correlation present in all members of the claimed genus.

With regard to the enablement Applicants argue that "the claimed invention does not read on the use of native (non-fusion) ubiquitin ligase polypeptides for recruitment of target polypeptides" (page 16, 2nd paragraph). For the clarification, the rejection concerns parts of the fusion protein that are not limited to native proteins. It is understood that the fusion protein per se does not occur in nature. Applicants further argue that "the invention is based upon recruitment per se of the target polypeptide to the ubiquitin ligase" (page 16, 3rd paragraph). However, said recruitment depends on ~~many factors such as specific components of the fusion protein linked together and a~~ cell where said fusion is used. Applicants assert that "the application teaches the surprising and useful observation that a selected polypeptide (such as retinoblastoma RB protein) can be targeted for degradation in vivo by simply expressing a fusion protein" (page 14, 2nd paragraph). However, applicants did not show that such RB degradation will be observed in any cell using a fusion of RB with any ubiquitin ligase. On the contrary, the state of the art suggests that such ~~task would require trial and~~ error. Further, if the observation is surprising, which it is for the specific examples taught by Applicants, its enablement should be commensurate in scope with said ~~examples.~~

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With regard to "live organism" and gene therapy applications for the instant invention, applicants arguments are not persuasive for the following reasons.

First, applicants define "in vivo" as a host cell not as a live organism (page 142). Second, at no occasion the specification mentions either "live organism" or "gene therapy"; third, Applicants' Remarks are focused on references that are not related to the current application whereas the state of art teaches that the field of gene therapy is highly unpredictable. The state of the art is reviewed by Verma et al. who teach that "in principle, gene therapy is simple. In practice, considerable obstacles have emerged." (Abstract) they teach that "there is still no single outcome that can point to as a success story" (page 239, 1st column, 2nd paragraph). "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression (page 239, 2nd column, 2nd paragraph). To override this problem is a case of trial and error for a given case.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

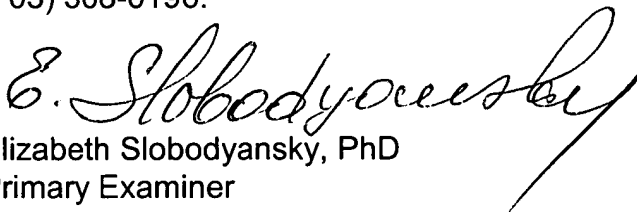
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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

  
Elizabeth Slobodyansky, PhD  
Primary Examiner

March 22, 2002